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DATA EVALUATION RECORD[1]

STUDY TYPE: 28-Day Dermal Toxicity – Rat; OPPTS 870.3200 [§82-2]; OECD 410.

PC CODE: 016331 **DP BARCODE:** D410187

TEST MATERIAL (PURITY): Momfluorothrin, Lot No.: 9CM0109G (95.7% a.i.)

SYNONYMS: S-1563

CITATION: Ogata, H. (2012). A 28-Day Repeated Dose Dermal Toxicity Study of S-1563 in Rats. Mitsubishi Chemical Medience Corporation. Kumamoto, Japan. Study No. P111028, August 20, 2012. MRID 49020010. Unpublished.

SPONSOR: Sumitomo Chemical Co., Ltd.

EXECUTIVE SUMMARY:

In a 28-day dermal toxicity study (MRID 49020010), S-1563 (Momfluorothrin, 95.7% a.i./Batch #9CM0109G) was applied to the shaved skin (approximately 4 cm x 5 cm) of Sprague-Dawley rats, 10/sex/dose, at dose levels of 0, 100, 300, 1,000 mg/kg bw/day, 6 hours/day for 5 days/week during a 28-day period.

No treatment related effects were observed on mortality, body weights, clinical signs, ophthalmoscopy, hematology, clinical chemistry, urinalysis, organ weights, macroscopic examination, or histopathology.

The NOAEL is 1,000 mg/kg/day (the limit dose).

This 28-day dermal toxicity study in the rat is **Acceptable/Non-Guideline** and satisfies the guideline requirement for a 28-day dermal toxicity study (OPPTS 870.3200; OECD 410) in rats. The study is considered to be non-guideline as the test material was applied to the gauze pad and not directly to the application site. However, this study is considered to be acceptable based on the following reasons 1) doses applied were up to the limit-dose 2) low dermal penetration (3.5%) was observed for momfluorothrin 3) this finding is consistent with the toxicology profile of many pyrethroids. No dermal hazard has been identified for fenpropathrin, zeta-cypermethrin, allethrin, deltamethrin, and prallethrin. Typically pyrethroids have a low absorption value of ≤ 5% and a high rate of metabolism.

1 Disclaimer: The attached Data Evaluation Record is a modified version of the Tier II Summary provided by Sumitomo Chemical Co. Ltd. Portions of this document may have been altered by the EPA reviewer.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test Material	S-1563, Momfluorothrin
Description:	Yellow solid
Lot/Batch:	9CM0109G
Purity:	95.7%
CAS#:	609346-29-4
Stability:	Expiration date: 13 January 2013
2. Vehicle	Water for injection
3. Test Animals	
Species	Rat
Strain	Crl:CD(SD)
Age	8 weeks (at start of administrations)
Weight	244.3 – 279.5 g (males) and 164.7 – 205.0 g (females) at start of administration
Source	Charles River Laboratories Japan, Inc. (Yokohama-shi, Japan)
Acclimation period	13 days (males); 14 days (females)
Diet	CRF-1 pellet diet (Oriental Yeast Co., Ltd) *ad libitum*
Water	Well water (disinfected with sodium hypochlorite ca. 2ppm) *ad libitum*
Housing	Stainless steel cages (W226× D346× H198 mm)
Environmental conditions	
Temperature	22.2 to 23.7°C
Humidity	43.2 to 60.3%
Air change	10-20 air changes per hour
Photoperiod	12-hour light/dark cycle

B. STUDY DESIGN:

1. **In life dates:** 28 February 2012 – 28 March 2012:

2. **Animal assignment:** Animals were assigned to the test groups (Table 1) by the stratified sequenced randomization method on the basis of body weight of the day, and it was confirmed that the weight variation of animals used was within ±20% of the mean weight for each sex (94.3% to 106.3% for males, and 90.9% to 109.6% for females).

TABLE 1: Study design

Test group	Dose (mg/kg bw/d)	# Male	# Female
Control	0	10	10
Low	100	10	10
Mid	300	10	10
High	1000	10	10

3. **Dose selection rationale:** The dose levels were selected based on the results from a single dose study where dermal administration of up to 2,000 mg/kg resulted in minimal effects. Therefore, the dose level of 1,000 mg/kg, the maximum dose level according to the guideline, was selected. The mid- and low-dose levels of 300 and 100 mg/kg were selected, respectively, with a common ratio of about 3 from the high dose level.

4. **Preparation and treatment of animal skin:** Shortly before the first application and weekly thereafter, the fur of each test animal was clipped from the dorsal area of the trunk over an area of at least 10% of the body surface (approximately 4 cm x 5 cm). The applied quantities of the test substance were adjusted weekly to individual animal body weight. The test substance/vehicle suspension was evenly dispersed on gauze patches that were then applied to the clipped skin, loosely covered with an elastic bandage. The dressings were removed after 6 hours and the application areas were cleaned with lukewarm water.

   Rats in the control group were exposed to the vehicle using the same procedure as described for the treated rats.

5. **Statistics:** Statistical analysis was performed using a computer system (MiTOX-PPL, Mitsui Zosen Systems Research Inc.). For numeric data, Bartlett's test was performed to compare the homogeneity of variances among groups (significant level: $p<0.05$). If the groups of data were homogeneous, Dunnett's multiple comparison test was performed relative to the control group. If the groups of data were heterogeneous, Steel's multiple comparison test was performed relative to the control group. Wilcoxon rank-sum test (Mann-Whitney's U test) was used for detailed clinical observations except for the number of rearings on the open field.
   For urinalysis (qualitative data), grades were converted to numerical values. The numerical values of each group were compared with those of the control group by Steel's multiple comparison test. Fisher's exact test was used for necropsy. For histopathological examination, grades were converted to numerical values. The numerical values of each group were compared with those of the control group by Wilcoxon rank-sum test (Mann-Whitney's U test). In either case, two-tailed test was used and levels of $p<0.01$ and $p<0.05$ were considered significant.

C. METHODS:

1. Observations:

1. Cage-side/Clinical/Neurological

Clinical signs and mortality were observed twice daily, before dosing and after dosing (after

removal of dosing formulation).

Detailed clinical observations were conducted before the start of the administration period and in Weeks 1, 2, 3, and 4 during the administration period (after removal of dosing formulation). The animals were randomized and arranged for examination, and home cage observation, hand-held observation, and observation on the open field were conducted. The following observations were made:

Home base observations:	Tremor, convulsion, respiration.
Hand-held observations:	Reactivity to handling, trauma, skin color, soiled fur, exophthalmos, palpebral closure, color of conjunctiva, secretion, lacrimation, salivation, piloerection, pupil size.
Open field observations:	Number of rearing (of forelimbs), arousal, urination, defecation, posture, respiration, gait, tremor, convulsion, stereotypy, bizarre behavior.

2. Bodyweight

Body weights were measured for all animals on Days 1, 8, 15, 22, and 28. The final bodyweight was measured for scheduled necropsy animals.

3. Food consumption

Food consumption was measured for all animals on Days 1, 8, 15, 22, and 28. The feeding vessels containing diet were weighed and set in the cage. On the next day, the remaining diet was weighed about 24 hours after feeding to calculate the food consumption.

4. Ophthalmoscopy

Ophthalmology was conducted on the day before the start of administration period and in Week 4 (before dosing). All animals before the start of administration period, and all animals in the control and the high dose groups in Week 4 were examined. Where abnormalities were observed, these animals were not used in the study.

Light reflex was confirmed using a direct ophthalmoscope after macroscopic observation of eye appearance. The cornea, iris, conjunctiva, lens, and vitreous body were inspected using a slit lamp after which the fundus oculi was inspected using a binocular indirect ophthalmoscope. Since there was no abnormality related to test substance in any animal used for the study, examination for middle and low dose groups was not conducted.

5. Hematology and Clinical Chemistry

Hematology

The animals were examined at necropsy after the end of the administration period. All animals were anesthetized with intraperitoneal injection of sodium pentobarbital and blood was collected from the posterior vena cava. For examination of the coagulation system, 0.9 mL of blood was collected into a glass tube containing trisodium citrate. For the examination of other items, remaining blood was collected into a container containing an anticoagulant (EDTA-2K). The animals were fasted for 16 to 23 hours before blood sampling. Parameters measured were: Leukocytes, Differential leukocyte count: (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils) Erythrocytes (RBC), Hemoglobin concentration (Hgb), Hematocrit, Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), Mean

corpuscular hemoglobin concentration (MCHC), Reticulocytes, Platelets, Prothrombin time (PT), Activated partial thromboplastin time (APTT).

Blood biochemistry

Blood (2 to 4 mL) was collected from the posterior vena cava for blood chemistry analysis. Parameters measured were: Total protein, Total bilirubin (T. bilirubin), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), γ-Glutamyl transpeptidase (γ-GTP), Alkaline phosphatase (ALP), Total cholesterol (T. Cholesterol), Triglycerides, Phospholipids, Glucose, Blood urea nitrogen (BUN), Creatinine, Inorganic phosphorus (IP), Calcium (Ca), Albumin, Albumin/globulin ratio (A/G ratio), Sodium (Na), Potassium (K), Chloride (Cl).

a. <u>Hematology</u>:

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count*	X	Reticulocyte count
X	Blood clotting measurements*		
X	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Recommended for 28-day dermal toxicity studies based on Guideline 870.3200

b. <u>Clinical chemistry</u>:

X	ELECTROLYTES	X	OTHER
X	Calcium	X	Albumin*
X	Chloride	X	Creatinine*
	Magnesium	X	Urea nitrogen*
X	Phosphorus	X	Total Cholesterol*
X	Potassium* (K)		Globulins
X	Sodium* (NA)	X	Glucose*
X	**ENZYMES** (more than 2 hepatic enzymes, eg., *)	X	Total bilirubin
X	Alkaline phosphatase (AP)*	X	Total protein*
	Cholinesterase (ChE)	X	Triglycerides
	Creatine phosphokinase		Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)	X	Phospholipids
X	Alanine aminotransferase (ALT/also SGPT)*		
X	Aspartate aminotransferase (AST/also SGOT)*		
X	Gamma glutamyl transferase (GGT)*		
	Glutamate dehydrogenase		
	Sorbitol dehydrogenase*		

* Recommended for 28-day dermal toxicity studies based on Guideline 870.3200

6. Urinalysis*: Urinalysis was conducted in week 4. Fresh urine samples were collected in the morning before dosing, using metabolic cages, and urine samples were collected successively for about 24 hours (pooled urine). The following parameters were measured: Volume, Gravity, Colour, Sodium (Na), Potassium (K) and Chloride (Cl) were all examined using 24 hour pooled samples. pH, protein, glucose, ketone body, bilirubin, occult blood, and urobilinogen were examined using fresh urine samples with Pretest 8aII (Wako Pure Chemical Industries Ltd.). Urine sediments were obtained by centrifugation and examined for epithelial cells, erythrocytes, leukocytes, casts, and crystals (phosphates and oxalates).

X	Appearance*	X	Glucose*
X	Volume*	X	Ketones
X	Specific gravity/osmolality*	X	Bilirubin
X	pH*	X	Blood / blood cells*
X	Sediment (microscopic)		Nitrate
X	Protein*		Urobilinogen

* Optional for 28-day dermal toxicity studies

7. Sacrifice and pathology: At the end of the administration period, animals were euthanized by exsanguination after blood sampling. The checked (X) organs and tissues were immediately examined macroscopically. Selected organs (XX) in addition, were weighed.

The following organs were collected and fixed in phosphate-buffered 10% formalin solution (the eyes, optic nerves, and harderian glands were pre-fixed in Davidson's solution, and the testes and epididymides were pre-fixed in Bouin's solution): Tongue, Larynx/Pharynx, Esophagus, Stomach, Duodenum, Jejunum, Ileum (with Peyer's patch), Caecum, Colon, Rectum, Submaxillary gland (with sublingual gland), Parotid gland, Liver, Pancreas, Trachea, Lung (with bronchi), Thymus, Submaxillary lymph node, Mesenteric lymph node, Spleen, Heart, Aorta, Kidney, Urinary bladder, Prostate, Seminal vesicle, Testis, Epididymis, Ovary, Uterus, Vagina, Mammary gland, Pituitary, Thyroid (with parathyroid), Adrenal, Brain (Cerebrum, cerebellum and medulla/pons), Spinal cord (Cervical to lumbar region), Optic nerve, Sciatic nerve, Eye, Harderian gland, M. biceps femoris, Sternum (with bone marrow), Femur (with bone marrow), Integument (lower abdominal), Nasal cavity, Treated site, Other gross lesions.

After necropsy, organs were weighed (absolute weight) and the ratio of organ weight to body weight (relative weight) was calculated on the basis of body weight measured on the day of necropsy. The paired organs were measured separately and the total weight was also calculated.

Samples of the above tissues from all animals in control and high dose groups were embedded, sectioned, stained with haematoxylin & eosin and examined histologically.

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	NEUROLOGIC
X	Tongue	X	Aorta, thoracic*	XX	Brain*+
X	Salivary glands*	XX	Heart*+	X	Peripheral nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	XX	Pituitary*+
X	Duodenum*	XX	Spleen*+	X	Eyes (optic nerve)*
X	Jejunum*	XX	Thymus*+	X	**GLANDULAR**
X	Ileum*			XX	Adrenal gland*+
X	Cecum*	X	**UROGENITAL**	X	Lacrimal gland
X	Colon*	XX	Kidneys*+	X	Parathyroid*
X	Rectum*	X	Urinary bladder*	XX	Thyroid*+
XX	Liver*+	XX	Testes*+	X	**OTHER**
	Gall bladder* (not rat)	XX	Epididymides*+		Bone (sternum and/or femur)
	Bile duct* (rat)	XX	Prostate*+		Skeletal muscle
X	Pancreas*	X	Seminal vesicles*		Skin* (treated & untreated areas)
X	**RESPIRATORY**	XX	Ovaries*+		All gross lesions and masses*
X	Trachea*	XX	Uterus*+		
XX	Lung*+	X	Mammary gland*		
X	Nose*				
X	Pharynx*				
X	Larynx*				

* Recommended for 28-day dermal toxicity studies based on Guideline 870.3200
\+ Organ weights required.

II. RESULTS:

A. OBSERVATION(s):

1. **Clinical signs of toxicity:** There were no test substance related clinical signs in either sex during the observation period. Frequent incidences of defecation were observed in males dosed at 1000 mg/kg/day. This finding was judged to be unrelated to the test substance administration, since a similar change was seen before the initiation of administration and the stool characteristic was normal in all animals.

2. **Mortality:** No mortality was observed in either sex at any test concentration.

3. **Neurological evaluations:** No neurological effects were reported in either sex at any test concentration.

4. **Dermal Irritation:** No dermal irritation was reported in either sex at any test concentration.

B. BODY WEIGHT AND WEIGHT GAIN: No effects on body weights were observed in either sex at any test concentration.

TABLE 2. Average body weights

Dose rate mg/kg/day	Body weights (g±SD)				
	Day 1	Day 8	Day 15	Day 22	Day 28
	Male				
0	261.1 ± 9.3	287.9 ± 15.3	312.6 ± 22.4	338.4 ± 25.9	356.6 ± 30.3
100	259.1 ± 10.5	288.3 ± 8.9	313.3 ± 8.5	337.3 ± 15.1	357.8 ±19.0
300	261.2 ± 10.1	287.8 ± 8.1	313.2 ± 8.6	331.9 ± 11.9	355.2 ± 11.7
1,000	259.7 ± 9.1	286.2 ± 15.7	309.9 ± 19.8	332.3 ± 23.8	354.0 ± 24.8
	Female				
0	184.3 ± 7.1	203.4 ± 9.7	214.5 ± 12.8	222.8 ± 14.1	323.9 ± 13.7
100	187.8 ± 8.1	203.5 ± 10.3	216.7 ± 10.2	224.4 ± 13.2	232.8 ± 13.2
300	183.2 ± 10.2	197.5 ± 12.3	204.1 ± 12.7	212.7 ±12.1	224.6 ± 13.5
1,000	183.1 ± 9.3	198.3 ± 8.0	208.9 ± 12.7	221.9 ± 14.5	233.5 ± 15.1

Data obtained from page 59 in the study report.
* Statistically different ($p < 0.05$) from the control.
** Statistically different ($p < 0.01$) from the control.

C. FOOD CONSUMPTION AND EFFICIENCY:

1. **Food consumption:** No effects on food consumption were observed in either sex at any test concentration.

2. **Food efficiency:** Not evaluated.

D. OPHTHALMOSCOPIC EXAMINATION: No change related to the test substance administration was seen in any animal in the 1000 mg/kg group.

Corneal opacity, particulate opacity in lens, focal opacity in lens and/or retinal fold were judged to be unrelated to the test substance administration, since they were comparable to the control values or were also seen before the initiation of administration.

E. BLOOD ANALYSES:

1. **Hematology:** In the 1000 mg/kg group, a significant decrease in erythrocytes was identified in females. However, this change was slight (< 5%), and reported to be within historical controls (data not provided). Additionally, no corresponding histopathology in the bone marrow was observed. Therefore, this change was not considered to be adverse.

2. **Clinical chemistry:** No effects on clinical chemistry were observed in either sex at any test concentration.

F. URINALYSIS: A very slight, but statistically significant ($p<0.05$), increase in protein was identified in females in the 1,000 mg/kg dose group. However, the study authors did not consider this to be related to test substance administration since individual animal values were within the variation of the controls, and since there were no test substance-related histopathological alterations noted in the urinary system.

G. SACRIFICE AND PATHOLOGY:

1. **Organ weight:** No treatment-related effects were identified on organ weights in either sex. Significant increases in relative weights of the right thyroid were identified for female rats in the 1,000 mg/kg dose group. However, as no differences were identified for total thyroid weight, and no corresponding histopathological effects were identified, this was not considered to be treatment-related. Additionally, the thyroid has not shown to be a target organ following oral exposure throughout the database.

2. **Gross pathology:** No macroscopic abnormalities were observed.

3. **Microscopic pathology**: No treatment-related histological abnormalities were observed. All abnormalities observed in the treatment groups were observed with similar incidence and degree as the control groups.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS: No death occurred among the males or females in the respective groups throughout the administration period. There was no toxicological change related to administration of the test substance in terms of the clinical observations, detailed clinical observations, body weights, food consumption, ophthalmology, urinalysis, hematology, blood biochemistry, necropsy, organ weights or histopathology.

Based on the above results, the NOAEL (no-observed-adverse-effect level) of S-1563 under the current study conditions is concluded to be 1000 mg/kg/day for both males and females.

B. REVIEWER COMMENTS: The reviewer agrees with the study authors. No adverse effects were identified following the administration of S-1563 to Wistar rats via dermal exposure.

The NOAEL is 1,000 mg/kg/day (the limit dose).

C. STUDY DEFICIENCIES: None